

I. Rejections under 35 U.S.C. 102(b)

A. Rejection of claims 4, 5, 10, and 11 as being anticipated by Erijta

Claims 4, 5, 10, and 11 stand rejected under 35 U.S.C. 102(b) as being anticipated by Erijta (NAR 14:8135-8153, 1986). Eritja is cited as teaching a method of making an oligonucleotide using a template containing a non-standard nucleotide (xanthine) by contacting the template with a mixture of nucleotide triphosphates and forming an oligonucleotide complementary to a portion of the template containing the xanthine by enzymatic polymerization, and incorporation of 9-(β -D-2'-deoxyribofuranosyl)-2-aminopurine triphosphate (dAPTP) opposite xanthine.

Claim 4, from which claims 5, 10, and 11 depend, is reproduced below:

4. *A method of making an oligonucleotide, the method comprising:*
providing a template oligonucleotide comprising a sequence of nucleotides,
the template comprising at least one non-standard nucleotide at a preselected site in
the sequence;
contacting the template with a mixture of nucleotide triphosphates, the mixture
comprising nucleotide triphosphates that are complementary to the nucleotides of the
template, wherein the nucleotide triphosphate complementary to the non-standard
nucleotide at the preselected site comprises a derivatized nucleotide; and
forming an oligonucleotide complementary to a portion of the template by
enzymatic polymerization of the nucleotide triphosphates in a sequence
complementary to the portion of the template.

Applicant respectfully submits that none of claims 4, 5, 10, or 11 is anticipated by the Erijta publication, because Erijta does not teach all of the limitations of claim 4. Claim 4 requires the incorporation of a derivatized nucleotide complementary to the non-standard base. The non-standard base xanthine is a purine with an acceptor-donor-acceptor (puADA) pattern of hydrogen bonding. As described throughout the specification, a non-standard purine or pyrimidine can base pair with a pyrimidine or purine, respectively, provided that the pyrimidine or purine has a hydrogen bonding pattern complementary to that of the non-standard base. In the specification (p. 6, paragraph 2), Applicant discloses pairing of complementary bases "following an expanded set of Watson-Crick rules: A pairs with T, G pairs with C, pyAAD pairs with puDDA, pyDAD pairs with puADA, pyDDA pairs with puAAD, and pyADD pairs with puDAA (Figure 2)."

The non-standard purine base xanthine has a puADA hydrogen bonding pattern, and a base complementary to xanthine would have a pyDAD hydrogen bonding pattern. Erijta does not disclose base pairing between xanthine and a complementary pyrimidine having a donor-acceptor donor hydrogen bonding pattern. In fact, Erijta discloses the misincorporation of the noncomplementary 2-aminopurine opposite xanthine to form a mispair, rather than a complementary base pair as required by claims 4, 5, 10, and 11.

Furthermore, claim 10 requires that the nucleotide triphosphates comprise at least one non-standard nucleotide triphosphate selected from the group consisting of pyDAD, puADA, pyAAD, puDDA, pyDDA, puAAD, pyADD and puDAA. Erijta does not teach including non-standard NTPs in the polymerization reaction.

In view of the foregoing, Applicant respectfully requests that the rejection of the claims under 102(b) as being anticipated by Erijta be withdrawn.

B. Rejection of claims 5 and 10 as being anticipated by Switzer or Piccirilli

Claims 5 and 10 were rejected under 35 U.S.C. 102(b) as being anticipated by Switzer *et al.*; claims 5 and 10 stand rejected under 35 U.S.C. 102(b) as being anticipated by Piccirilli *et al.* The Examiner stated that claims 5 and 10 are not entitled to the claim of priority to the original application, but are only entitled to claim priority back to U.S. Serial No. 08/775,401, filed December 31, 1996, because the original applications application did not describe the isoG and isoC in terms of their base pairing patterns (puDDA and pyAAD).

Applicants respectfully submit that the present application is entitled to a claim of priority to the original application because, although the particular abbreviations "puDDA" and "pyAAD" were not used in the original application, the concept was disclosed. For example please see Figs. 2 and 4 of U.S. Serial No. 07/594,290, filed October 9, 1990, now issued as U.S. Patent No. 5,432,272. Fig. 2 illustrates the various acceptor/donor hydrogen bond patterns between specific non-standard purine or pyrimidine bases, and Fig. 4 provides the generalized structures of four non-standard base pairs formed between eight non-standard bases. In Fig. 2 of US Patent No. 5,432,272, the pyrimidines (py) appear on the left hand side, and the purines (pu) appear on the right hand side. As Fig. 2 illustrates, the non-standard pyrimidines have donor or acceptor groups, given in order from the major to minor groove, which fall into one of four patterns: "Acceptor Acceptor Donor" (pyAAD), a "Donor, Acceptor Donor" (pyDAD), a "Donor Donor Acceptor" (pyDDA), or an "Acceptor Donor Donor" (pyADD). Similarly, the non-standard purines have donor or acceptor groups, given in order from the major to minor groove, which fall into one of four patterns: "Donor Donor

Acceptor" (puDDA), an "Acceptor Donor Acceptor" (puADA), an "Acceptor Acceptor Donor" (puAAD), or a "Donor Acceptor Acceptor" (puDAA). This concept was fully disclosed in the original application. The explanation of the shorthand abbreviations (py, pu, A, and D) (page 10, lines 3-7 of the instant application) is entirely consistent with and supported by the disclosure of the U.S. Serial No. 07/594,290.

In view of the foregoing, Applicants respectfully request that the 102(b) rejection of claims 5 and 10 over Switzer and Piccirilli be withdrawn.

Rejections under 35 U.S.C. 102(a)

Claims 4, 6, 8-9, and 11-14 were rejected under 35 U.S.C. 102(a) as being anticipated by Switzer *et al.* (J. Am. Chem. Soc. 111:8322-8323, 1989); claims 4, 6, 8-9, and 11-14 stand rejected under 35 U.S.C. 102(a) as being anticipated by Piccirilli *et al.* (Nature 343:33-37; 1990). Both Switzer *et al.* and Piccirilli *et al.* were published less than one year prior to the filing of this application. Submitted herewith are declarations of Steven A. Benner, Ph.D., the sole inventor on the subject application, under 35 U.S.C. 1.132. The declarations state that Dr. Benner is a co-author on the Switzer publication and on the Piccirilli publication, each of which describes, in part, the work set forth in the present application. The declaration further states that Dr. Benner is the sole inventor of claims 4-14, and that the other co-authors on the Switzer and Piccirilli publications did not make an inventive contribution to the subject invention. Applicants therefore request that the rejection of claims under 35 U.S.C. 102(a) over Switzer *et al.* or Piccirilli *et al.* be withdrawn.

Rejections under 35 U.S.C. 103(a)

Claims 7-9, which depend from claim 4, stand rejected under 35 U.S.C. 103(a) as being anticipated by Eritja *et al.* The Examiner asserts that incorporation of labeled nucleotides into oligonucleotides by primer extension is well known.

Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness, which requires (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) the art reference or combination of references must teach all of the claim limitations (MPEP 2142).

As Applicant pointed out above in the discussion of the rejection of claims 4, 5, 10, and 11 under 102(b), Eritja does not teach all of the limitations of claim 4. Specifically,

Erijta does not teach the incorporation of a derivatized nucleotide complementary to the non-standard base, as required by claim 4. Therefore, Erijta does not teach all of the claim limitations of claims 7-9, which depend from and further limit claim 4.

Claim 7 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Switzer *et al.* For the reasons discussed above under the section concerning 35 U.S.C. 102(a), Applicants respectfully request that Switzer *et al.* be removed as a reference and that the rejection under 35 U.S.C. 103(a) be withdrawn.

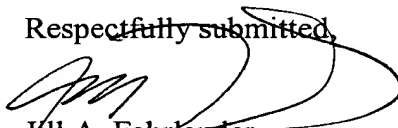
Rejections under the judicially created doctrine of obviousness-type double patenting

All claims stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U.S. Patent Nos. 5,432,272, 6,001,983, and 6,037,120. Applicants submit herewith a terminal disclaimer disclaiming the terminal part of the statutory term of any patent granted on the subject application beyond the expiration date of the full statutory term of U.S. Patent No. 5,432,272, 6,001,983, and 6,037,120. The disclaimer is executed by the Steven A. Benner, who currently owns the entire right and interest to the claimed invention.

As the application is now in condition for allowance, Applicants request allowance of the claims. Should the Examiner feel that any other point requires consideration or that the form of the claims can be improved, the Examiner is invited to contact the undersigned at the number listed below.

Applicants request a three-month extension of time extending the period for response from October 5, 2001 to January 5, 2002. This submission is accompanied by a check in the amount of \$515 for the three-month extension of time fee and for the terminal disclaimer filing fee. Please charge any additional fee due or credit any overpayment of fees to Deposit Account No. 50-0842.

Respectfully submitted,



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